Handbook of Pharmaceutical Excipients

FOURTH EDITION

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Hypromellose

1 Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose

2 Synonyms

Benecel MHPC; cellulose, hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*; *Spectracel 6*; *Spectracel 15*; *Tylopur*.

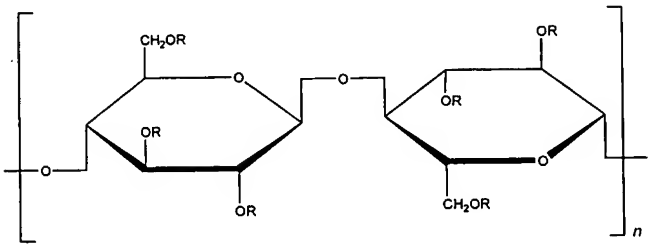
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula Molecular Weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

5 Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6 Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,[1] in film-coating,[2–7] and as an extended-release tablet matrix.[8–12] Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8 Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

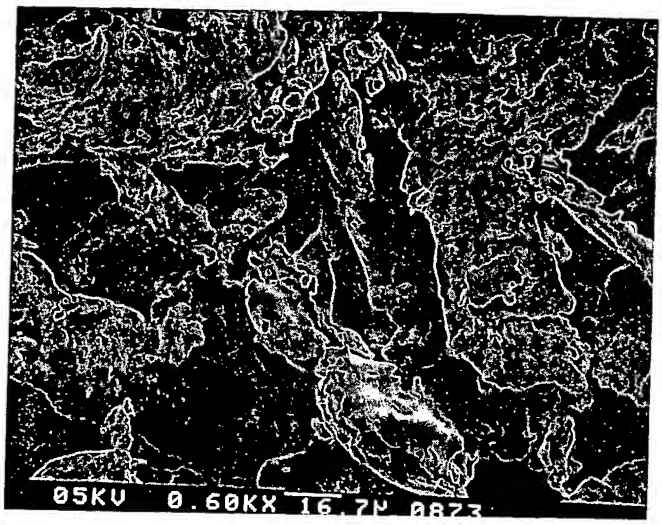
9 Pharmacopeial Specifications

See Table I.

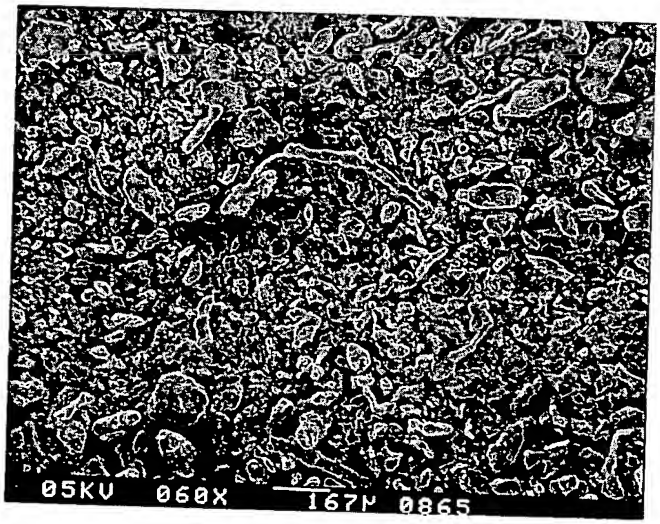
10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.
Ash: 1.5–3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (bulk): 0.341 g/cm^3
Density (tapped): 0.557 g/cm^3
Density (true): 1.326 g/cm^3
Melting point: browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.
Moisture content: hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air. *See* Figure 1.

SEM: 1
Excipient: Hypromellose
Manufacturer: Dow Chemical Co.
Lot No.: ME20012N11
Magnification: 600 ×
Voltage: 5 kV



SEM: 2
Excipient: Hypromellose
Manufacturer: Dow Chemical Co.
Lot No.: ME20012N11
Magnification: 60 ×
Voltage: 5 kV



Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. *See also* Section 11.
Specific gravity: 1.26

Table I: Pharmacopeial specifications for hypromellose.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
pH (1% w/w solution)	5.0–8.0	5.5–8.0	—
Apparent viscosity	+	+	+
Loss on drying	≤5.0%	≤10.0%	≤5.0%
Residue on ignition	≤1.5%	—	—
For viscosity grade >50 mPa s	—	—	≤1.5%
For viscosity grade ≤50 mPa s	—	—	≤3.0%
For type 1828 of all viscosities	—	—	≤5.0%
Sulfated ash	—	≤1.0%	—
Chlorides	≤0.284%	≤0.5%	—
Heavy metals	≤10 ppm	≤20 ppm	≤0.001%
Iron	≤100 ppm	—	—
Arsenic	≤2 ppm	—	—
Organic volatile impurities	—	—	+
Methoxy content			
Type 1828	—	—	16.5–20.0%
Type 2208	19.0–24.0%	—	19.0–24.0%
Type 2906	27.0–30.0%	—	27.0–30.0%
Type 2910	28.0–30.0%	—	28.0–30.0%
Hydroxypropoxy content			
Type 1828	—	—	23.0–32.0%
Type 2208	4.0–12.0%	—	4.0–12.0%
Type 2906	4.0–7.5%	—	4.0–7.5%
Type 2910	7.0–12.0%	—	7.0–12.0%

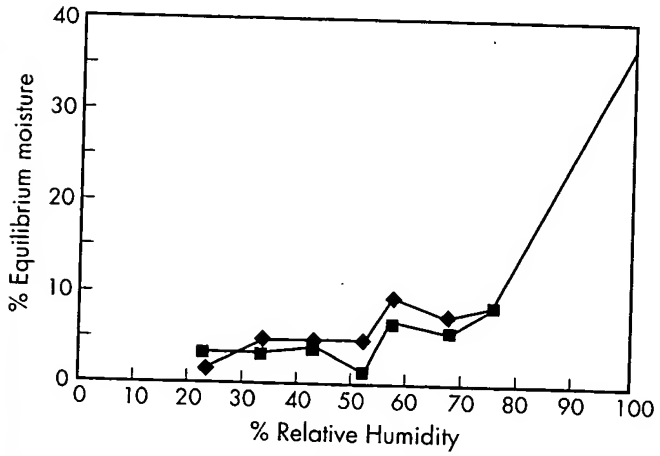


Figure 1: Absorption–desorption isotherm for hypromellose.
◆: Sorption
■: Desorption

Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions; *see* Table II.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of *Methocel* (Dow Chemical Co.). Viscosities measured at 20°C.

Methocel grade	Nominal	Viscosity (mPa s)
K100LVP	100	80–120
K4M	4000	3000–5600
K15MP	15000	12000–21000
K100MP	100000	80000–120000
E4MP	4000	3500–5600
E10MP CR	10000	8000–13000
E3 PREM.LV	–	2.4–3.6
E5 PREM.LV	–	4–6
E6 PREM.LV	–	5–7
E15 PREM.LV	–	12–18
E50 PREM.LV	–	40–60
K3 PREM.LV	–	2.4–3.6

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.[13] However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

13 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14 Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.[14] The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.[15]

LD_{50} (mouse, IP): 5 g/kg[16]
LD_{50} (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose; hypromellose phthalate; methylcellulose.

18 Comments

Powdered or granular, surface-treated grades of hypromellose are also available that are dispersible in cold water. These are not recommended for oral use.

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